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Review

Comparison of the relapse rates in seizure-free patients in whom antiepileptic therapy was discontinued and those in whom the therapy was continued: A meta-analysis

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ABSTRACT

About 70% of patients with epilepsy can be seizure-free with an appropriate treatment. When the seizures are under control, discontinuation of the antiepileptic drugs (AEDs) can help avoid their side effects; however, it may increase the risk of relapse. Some studies have compared the relapse rates between patients in whom AEDs have been continued and those in whom AEDs have been discontinued. However, it is not clear whether AED discontinuation causes a higher seizure recurrence rate. This meta-analysis aimed mainly to determine whether the seizure recurrence rate was different between seizure-free patients in whom AEDs were continued and those in whom AEDs were discontinued. The I^2 value was used for assessing the heterogeneity; the Mantel–Haenszel test was used to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). Seven cohort studies and randomized controlled trials (RCTs) met the inclusion criteria. The study quality evaluation was performed respectively using the Newcastle–Ottawa Scale and the Jadad scale. A total of 1253 patients were included. The relapse rate was higher in patients in whom AEDs were discontinued than in those in whom the AED treatment was continued.

Furthermore, we also compared the epilepsy recurrence rates after AED discontinuation between seizure-free patients who were on monotherapy with different AEDs (carbamazepine, phenytoin, sodium valproate, and phenobarbitone/primidone). Four studies and 625 patients were included in this analysis. The epilepsy recurrence rates did not significantly differ between the patients on different AED treatment.

1. Introduction

Epilepsy is a chronic disease that is defined as an occurrence of two or more unprovoked seizures [1]. It affects more than 50 million people worldwide. Most (nearly 80%) of the patients with epilepsy live in low- and middle-income countries, and 75% of these patients do not get treatment [1]. Epilepsy represents 0.7% of the global burden of disease [2]. All these numbers indicate the degree of impact this disease has on the patients' quality of life.

One of the reasons why many patients with epilepsy do not receive treatment must be the therapeutic expenses. With an antiepileptic drug (AED) treatment, 70% of the patients with epilepsy can be seizure-free [1,3]. If the AEDs can be discontinued after the patients are seizure-free, the therapeutic expenses would be less, and there may be more low- or middle-income patients willing to get treatment for epilepsy.

The discontinuation of AEDs not only decreases the cost of the treatment, but it also improves the quality of life of the patients, since the long-term use of AEDs has many side effects, such as cognitive problems [4], cosmetic effects [5], ataxia [6], tremor [7], and sedation [8].

However, seizures may relapse after discontinuation of the AEDs [9–13], which is one of the greatest concerns for doctors and patients when considering AED treatment withdrawal. Yet, it is not well known whether discontinuing the AEDs in patients who are seizure-free really increases the seizure recurrence rate. Different studies [9,13,14–22] have different answers to this question. The correlation between AED treatment withdrawal and seizure relapse is controversial. Therefore, this meta-analysis aimed to estimate the relation between AED discontinuation and epilepsy relapse in patients with epilepsy who are seizure-free.

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2. Methods

2.1. Literature search

We performed a literature search in the PubMed, Cochrane library, and EMBASE databases in April 2019, and the period used for the search was before April 13, 2019. The authors reviewed all the searched articles and some relevant studies from the reference list of the included study. Two of the authors (WJ and HP) independently assessed all the articles and extracted the data. Any disagreements were resolved by discussion.

2.2. Search words

The search query terms and their synonyms used in this meta-analysis were “anticonvulsants”, “antiepileptic drugs”, “anticonvulsive agents”, “agents, anticonvulsive”, “anticonvulsive drugs”, “drugs, anticonvulsive”, “anticonvulsant drugs”, “drugs, anticonvulsant”, “antiepileptic agents”, “agents, antiepileptic”, “antiepileptics”, “antiepileptic drugs”, “drugs, antiepileptic”; “withdrawal”; “epilepsy”, “epilepsies”, “seizure disorder”, “seizure disorders”, “awakening epilepsy”, “epilepsy, awakening”, “epilepsy, cryptogenic”, “cryptogenic epilepsies”, “cryptogenic epilepsy”, “epilepsies, cryptogenic”, “aura”, “auras”; “recurrence”, “recurrences”, “recrudescence”, “recrudescences”, “relapse”, “relapses”; “seizure-free”, and “seizure free”.

2.3. Selection criteria

The inclusion criteria were as follows: (1) original articles, (2) articles that reported on patients in whom AED treatment was withdrawn/continued after they became seizure-free, (3) articles that reported the number of patients with a relapse both among those in whom AED treatment was withdrawn and those in whom AED treatment was continued after they became seizure-free, (4) the study type was a randomized controlled trial (RCT) or a cohort study, (5) articles published before April 13, 2019, and (6) articles written in English.

We excluded articles that reported on patients in whom the diagnosis of epilepsy was not confirmed.

2.4. Data extraction

Two authors (WJ and HP) reviewed the searched studies and decided which should be included in the analysis. Any disagreements were resolved by discussion. The data we collected from the included studies were as follows: name of first author, publication year, study type, epilepsy type, seizure-free period, follow-up duration, patients' age at the time of joining the study, gender, the total number of patients in whom AED treatment was withdrawn and those in whom AED treatment was continued, and the number of patients who experienced recurrence both among those in whom AED treatment was withdrawn and those in whom AED treatment was continued.

2.5. Assessment of risk of bias in the included studies

The risk of bias of the observational studies and RCTs was assessed according to the Newcastle–Ottawa Quality Assessment Scale [23] (NOQAS) and Jadad scale (5 point) [24], respectively, by two authors (WJ and HP). Depending on the scores, the quality of the observational studies was divided into three levels: score 1–3 was regarded as a low-quality level, score 4–6 was regarded as a medium-quality level, and score 7–9 was regarded as a high-quality level. The quality of the RCTs was divided into two levels: score 1–2 was regarded as a low-quality level and score 3–5 was regarded as a high-quality level.

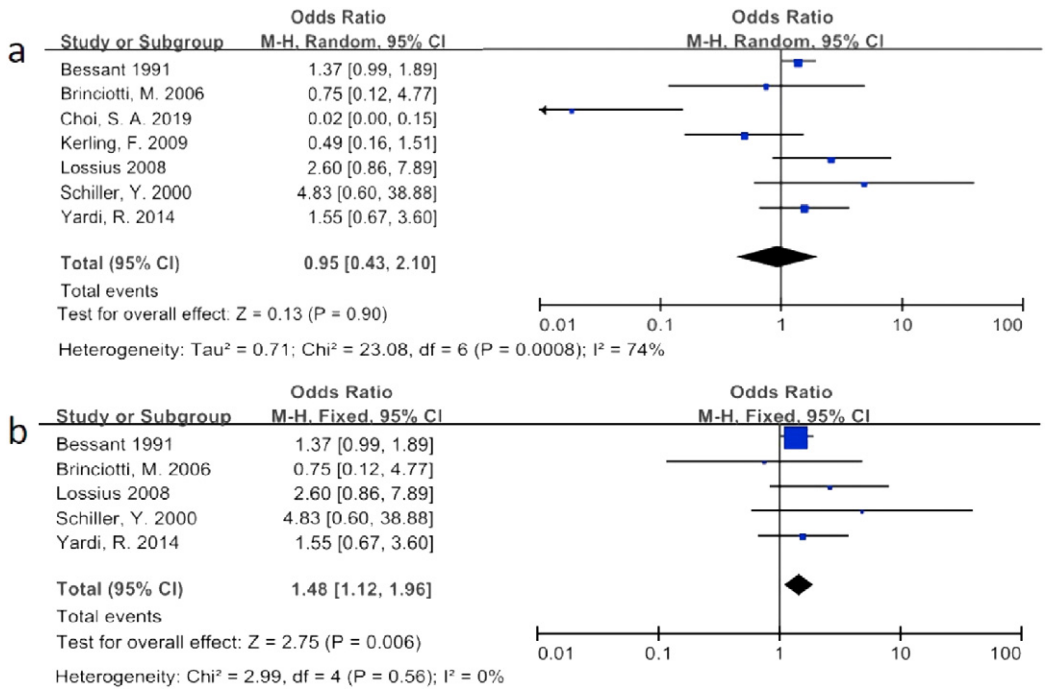

Fig. 1. Forest plot of the comparison of withdrawal AED vs continue AED and the seizure recurrence rate during follow-up years. a. Forest plot of 7 included studies. Significant heterogeneity existed among studies ($P = 0.0008$, $I^2 = 74\%$), the pooled OR was calculated using random effect model and no significant differences on relapse rates between withdrawal AED and continue AED (OR (95% CI): 0.95 (0.43–2.10), $P = 0.90$). b. Forest plot of 5 low selection bias studies. Heterogeneity did not exist among studies ($P = 0.56$, $I^2 = 0\%$), the pooled OR was calculated using fixed effect model. There were less relapse rates in seizure-free patients with continued antiepileptic therapy while compared with discontinued therapy (OR (95% CI): 1.48 (1.12–1.96), $P = 0.006$). Horizon axis represents odd ratio value; Last name of the first author and published year of study was utilized in study column; The diamond denotes the OR with corresponding 95% CI for the pooled effect, the square with the line denotes the OR with corresponding 95% CI for each study. AEDs: antiepileptic drugs, OR: odd ratio, CI: confidence interval, M-H: Mantel–Haenszel.

Table 1
Observational study quality assessment according to the Newcastle–Ottawa Quality Assessment Scale.

Study	Author	Year	Selection				Comparability		Outcome			Total
			1	2	3	4	1	2	1	2	3	
Retrospective cohort	Choi, S. A.	2019	1	0	1	1	0	0	1	1	1	6
Retrospective cohort	Schiller, Y.	2000	1	1	1	1	0	0	1	1	1	7
Prospective cohort	Kerling, F.	2009	1	0	1	1	1	0	1	1	1	7
Prospective cohort	Yardi, R.	2014	1	1	1	1	1	0	1	1	1	8
Prospective cohort	Brinciotti, M	2006	1	1	1	1	0	0	1	1	1	7

2.6. Statistical analyses

Data analysis was performed using RevMan 5.3 software. I squared (I^2) value was used for assessing the statistical heterogeneity; $I^2 > 50\%$ was considered to be with a high heterogeneity. In the beginning, a fixed model of analysis was used to account for the heterogeneity. If $I^2 > 50\%$, the random effects model was used. Mantel–Haenszel's method was used to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). The OR > 1 represents less relapse rates in seizure-free patients with continued antiepileptic therapy while compared with discontinued therapy. In contrast, OR < 1 means more relapse rates in seizure-free patients with continued antiepileptic therapy while compared with discontinued therapy. Statistical significance was accepted at $P \le 0.05$.

3. Results

3.1. Search results

A total of 274 studies were found with the electronic search; 86, 153, and 35 studies were found in PubMed, EMBASE, and Cochrane library, respectively. There were 197 studies left after 77 duplicate studies were excluded. After screening the title and abstract of the studies, 187 studies were excluded in this round; among the 187 rejected studies, 36 of them were reviews, 25 of them were not written in English, 29 articles were unrelated, and in 97 articles, there were no related relapse rate available. The investigators assessed the full text articles of the remaining ten studies for eligibility; four studies were excluded because full texts were not available, and the six full-text studies were included. After reviewing the reference lists of the relevant studies, another study was included. Finally, seven studies were included in the analysis.

The methodological quality of the seven included studies was assessed using the NOQAS and Jadad scales. The results are shown in Tables 1 and 2. Among the seven studies, six studies received high quality rating and one study received a medium quality rating. Among the observational studies, two studies only received three scores; however, the remaining observational studies received full scores in the selection part. Regarding the RCTs, since they were randomized, they also received full scores if the selection standards of observational studies were used.

In Table 3, the characteristics of the seven included studies are presented. Two studies were retrospective cohort studies, three studies were prospective cohort studies, and two studies were RCTs. The epilepsy types were different; three of the studies investigated partial epilepsy [15,16,18], three studies included both generalized and partial epilepsy [9,14,19], and in one study, the type of epilepsy was not specified [17]. Most of the participants enrolled in the included studies had more than 1-year seizure-free time [9,14,16,17,19]; the exact seizure-free time was not clearly stated in one of the studies [18]. All the patients enrolled in the included studies were followed up for at least 1 year. One study included only children [15], three studies included only adults [9,14,17], and three studies included both children and adults [16,18,19]. We recorded the number of total patients and the number of patients with a relapse both among those in whom AED treatment was withdrawn and those in whom AED treatment was continued group in all studies. The time to relapse was different among the studies; the patients were evaluated for recurrence one or two years after withdrawal of the AEDs [9,16,18], four to five years after withdrawal of the AEDs [14,15,17], or more than 10 years after withdrawal of the AEDs [19].

3.2. Relapse results in all included studies

Seven studies and 1318 patients were included in this analysis. We compared the number of patients with a relapse among patients in whom AED treatment was withdrawn with that of patients in whom AED treatment was continued. As shown in Fig. 1a, the I^2 was 74% ($P = 0.0008$), the OR was 0.95 (95% CI: 0.43–2.1, $P > 0.05$) using random effect model. In Fig. 2a, the nonsymmetrical funnel plot suggests that publication bias may exist.

3.3. Relapse results of low-selective-bias studies

The results from all seven included studies showed that the patients in whom AED treatment was discontinued did not have a higher relapse risk, but the heterogeneity was high. Thus, we performed a sensitivity analysis. Since two of the seven included studies only received three scores in the selection part during the study quality assessment, and the other five studies received full scores, a subgroup analysis was performed including only the low-selective-bias studies that received full scores in the selection part during the study quality assessment. The subgroup analysis results are presented in Fig. 1b. In comparing the number of patients with AED treatment withdrawal with those in whom AED treatment was continued, the OR was 1.48 (95% CI: 1.12–1.96, $P < 0.05$) and I^2 was 0% ($P = 0.56$), which means that the heterogeneity was acceptable. In Fig. 2b, we presented the funnel plot for this subgroup, which showed that all five studies existed inside of the funnel. The analyzed results of the low-selective-bias studies were different from those of all seven included studies, and the heterogeneity I^2 changed from 74% to 0%.

3.4. Epilepsy relapse and type of AEDs

In the study by Lossius et al., the prior use of carbamazepine was correlated with a greater chance of remaining seizure-free after AED treatment discontinuation [9]. We, therefore, performed a meta-analysis to compare the epilepsy relapse rate between seizure-free patients treated with different AEDs before withdrawal of the AEDs. The keywords for this meta-analysis were the same as those listed above. Among all the

Table 2
RCT study quality assessment according to the Jadad scale.

Study type	Author	Year	Randomization	Double blinding	Withdrawals and dropouts	Total
RCT	Bessant	1991	2	0	1	3
RCT	Lossius, M. I.	2008	1	2	1	4

Table 3
Characteristics of included studies.

Author	Year	Study type	Epilepsy type	Seizure-free period	Follow-up years since AEDs withdrawal or surgery	Age mean (range) years	Gender Male (%)	Duration between AEDs withdrawal or surgery and counting relapse patients number time	AEDs withdrawal patients		AEDs continue patients	
									No. of patients	No. of patients for recurrence	No. of patients	No. of patients for recurrence
Choi, S. A.	2019	Retrospective cohort study	Partial epilepsy (focal cortical dysplasia)	≥6 months	≥2	10.2 (1.1–16.8)	Not clear	Mean 4.5 years	40	14	30	29
Schiller, Y.	2000	Retrospective cohort study	Partial epilepsy	≥1 year	2	31.9 (9–55)	49	2 years	84	12	30	1
Kerling, F.	2009	Prospective cohort study	Epilepsy	1 year	5	35 (16–62)	40	5 years	34	8	26	10
Yardi, R.	2014	Prospective cohort study	Partial epilepsy (temporal lobe epilepsy)	Not clear	Average 4.62 (0.5–16.7)	34.7 (1–74.3)	48	2 years	65	12	110	14
Brinciotti, M	2006	Prospective cohort study	Generalized and partial	≥2 years	Average 13.9 (6.4–27.6)	21.4 (11.2–35.5)	40	Mean 13.9 years	10	2	20	5
Bessant	1991	RCT	Generalized and partial	≥2 years	4	31 (19–45)	Not clear	4 years	393	133	327	89
Lossius, M. I.	2008	RCT	Generalized and partial	≥2 years	1	38 (18–66)	47	1 year	72	11	77	5

274 studies searched from the databases, and by reading related reference articles, we found four studies that analyzed the correlation between the types of AEDs and epilepsy recurrence. The patients in these studies received monotherapy and were seizure-free for at least 2 years prior to withdrawal of the AED treatment. The epilepsy recurrence rates were measured for the different AEDs, and the cohort study quality assessment, RCT study quality assessment, and the characteristics of the four studies are shown in Supplementary Table 1, Supplementary Table 2, and Supplementary Table 3, respectively. We compared the epilepsy recurrence rates of different AEDs. Four studies including 625 participants compared the epilepsy recurrence rates after treatment with carbamazepine with those after treatment with valproate [9,10,12,13]; the results showed that the OR for carbamazepine was 0.72 (95% CI: 0.52–1.01, P > 0.05, Fig. 3 1.2.1). Three studies including 516 participants compared the epilepsy recurrence rates after treatment with carbamazepine with those after treatment with phenytoin [9,12,13], and the OR for carbamazepine was 0.87 (95% CI: 0.60–1.26, P > 0.05, Fig. 3 1.2.2). Three studies including 437 participants compared the epilepsy recurrence rates after treatment with carbamazepine with those after treatment with phenobarbital [9,10,12], and the OR for carbamazepine was 0.93 (95% CI: 0.60–1.45, P > 0.05, Fig. 3 1.2.3). Three studies including 458 participants compared the epilepsy recurrence rates after treatment with valproate with those after treatment with phenytoin, and the OR for valproate was 1.08 (95% CI: 0.74–1.59, P > 0.05, Fig. 3 1.2.4). Three studies including 398 participants compared the epilepsy recurrence rates after treatment with valproate with those after treatment with phenobarbital, and the OR for valproate was 1.37 (95% CI: 0.84–2.23, P > 0.05, Fig. 3 1.2.5). There was no heterogeneity reported in all the above subgroups (I^2 < 50%, Fig. 3).

3.5. Conclusion

Continuation of AED treatment has a lower epilepsy recurrence rate than the withdrawal of AED treatment in patients with epilepsy who are in remission; and no significant difference in the epilepsy recurrence

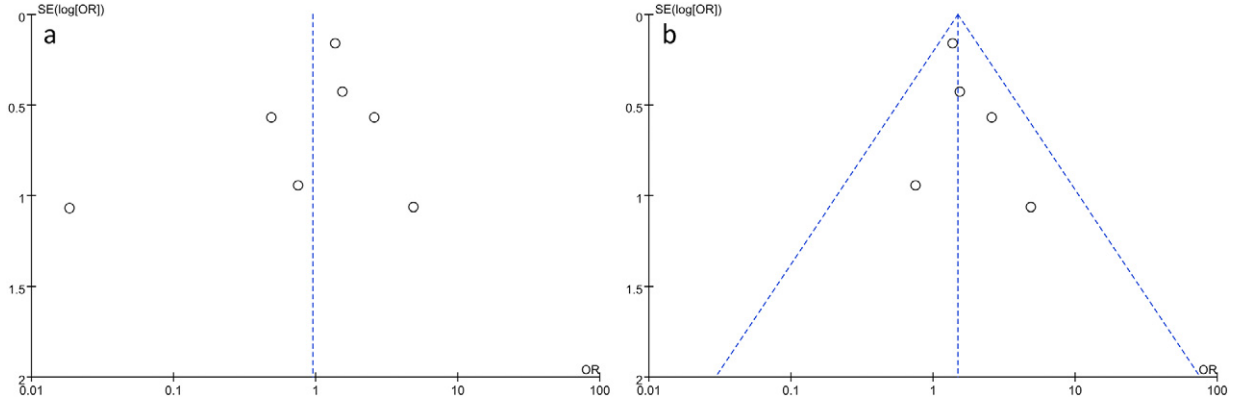

Fig. 2. Funnel diagram for publication bias test. Panel a. Funnel diagram for all 7 included studies. The funnel plot is not symmetrical; publication bias may exist. Panel b. Funnel diagram of 5 low selection bias studies. The funnel plot is symmetrical, suggesting there is no significant publication bias in the meta-analysis. Natural log transformation of odds ratio as y-axis; odds ratio as x-axis. Each circle represents a separate study. OR: odds ratio; AED: antiepileptic drugs.

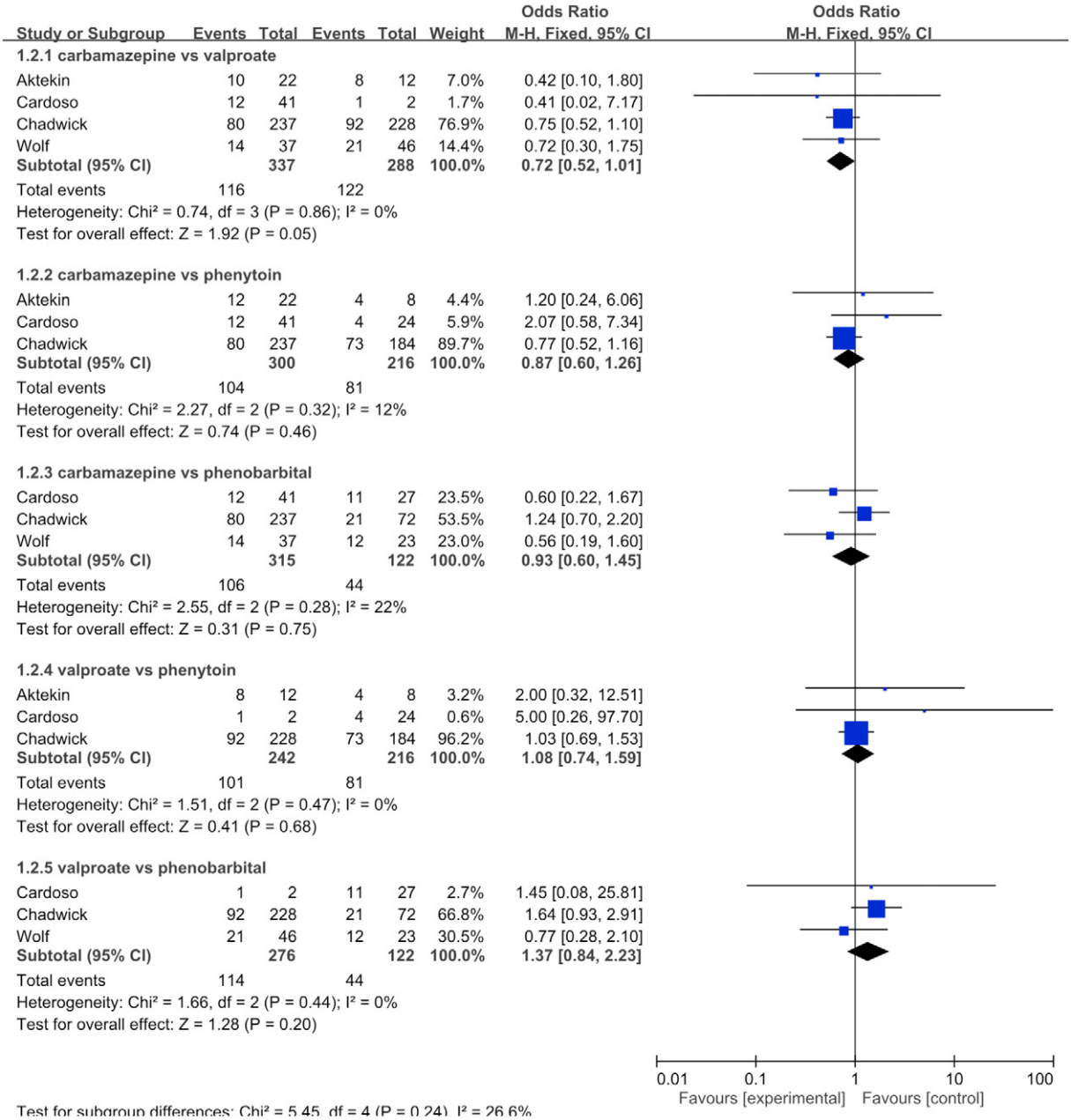

Fig. 3. Subgroup analysis on the correlation between the used AED types before withdrawal and epilepsy relapse. (1.2.1) Forest plot of the comparison between carbamazepine vs valproate. Based on the nonsignificant heterogeneity among studies ($P = 0.86$, $I^2 = 0\%$), the pooled OR was calculated using fixed effect model, there were no significant differences on relapse rates between carbamazepine and valproate (OR (95% CI): 0.72 (0.52–1.01), $P = 0.05$). (1.2.2) Forest plot of the comparison between carbamazepine vs phenytoin. Based on the nonsignificant heterogeneity among studies ($P = 0.32$, $I^2 = 12\%$), the pooled OR was calculated using fixed effect model, there were no significant differences on relapse rates between carbamazepine and phenytoin (OR (95% CI): 0.87 (0.60–1.26), $P = 0.46$). (1.2.3) Forest plot of the comparison between carbamazepine vs phenobarbital. Heterogeneity among studies was not significant ($P = 0.28$, $I^2 = 22\%$), the pooled OR was calculated using fixed effect model, there were no significant differences on relapse rates between carbamazepine and phenytoin (OR (95% CI): 0.93 (0.60–1.45), $P = 0.75$). (1.2.4) Forest plot of the comparison between valproate vs phenytoin. Heterogeneity among studies was not significant ($P = 0.47$, $I^2 = 0\%$), relapse rates between carbamazepine and phenytoin was not significant (OR (95% CI): 1.08 (0.74–1.59), $P = 0.68$). (1.2.5) Forest plot of the comparison between valproate vs phenobarbital. There was no significant heterogeneity ($P = 0.44$, $I^2 = 0\%$) and no significant differences on relapse rates between carbamazepine and phenytoin (OR (95% CI): 1.37 (0.84–2.23), $P = 0.20$). Horizon axis represents odd ratio value; Last name of the first author and published year of study was utilized in study column; The diamond denotes the OR with corresponding 95% CI for the pooled effect, the square with the line denotes the OR with corresponding 95% CI for each study. AEDs: antiepileptic drugs, OR: odd ratio, CI: confidence interval, M-H: Mantel–Haenszel.

rates between the different AEDs (carbamazepine, valproate, phenytoin, and phenobarbital).

4. Discussion

Many researchers have studied the relationship between the discontinuation of the AED treatment and epilepsy relapse; however, most of them focused on the possible risk factors for epilepsy recurrence. Some studies pointed out that an abnormal electroencephalogram (EEG) was a risk factor for relapse [25–30]. Several studies investigated whether the length of the seizure-free interval before AED treatment withdrawal was a risk factor for disease relapse [25,31,32]. One study indicated that multiple tumor resections may be a risk factor for relapse [33], and many other studies also focused on other possible risk factors.

However, only few studies have focused on the correlation between the AED treatment withdrawal itself and epilepsy recurrence in patients who are seizure-free for a period of time, and the current results are controversial.

Lamberink et al. [34] using nomograms identified several predictors of seizure recurrence in the patients with epilepsy who withdrew AEDs. However, Lamberink et al. did not compared with control group of continuing antiepileptic drug treatment, and they did not discuss the type of AEDs whether a predictor for predicting seizure recurrence. Recommendation from guidelines of the Italian League Against Epilepsy on withdrawal of AEDs is consistent with our analysis. The guideline suggests that the decision to stop or withhold treatment in a seizure-free patient is not affected by the type of drug to be removed with an evidence level of C [35]. Our study would improve the evidence strength with more populations included. Schmidt reported that the question "does AED discontinuation increase the risk of seizures compared with continued treatment?" may help to evaluate the risks involved in AED discontinuation in seizure-free patients [36]. But the guidelines of the Italian League Against Epilepsy did not answer this question. Our results, it is better to continue AEDs treatment in seizure-free patients to decrease seizure relapse risk.

The result of this meta-analysis is that the continuation of AED treatment has a lower epilepsy recurrence rate than the withdrawal of AED treatment in patients with epilepsy who are in remission. In all seven included studies, the relative OR of AED treatment withdrawal was 1.12 ($P > 0.05$), but in the 5 low-selective-bias studies, the relative OR of AED treatment withdrawal was 1.48 ($P < 0.05$). Since the calculated heterogeneity was high ($I2 = 74\%$) for all the seven included studies, and heterogeneity was nonexistent in the five low-selective-bias studies ($I2 = 0\%$), this study demonstrated that the withdrawal of AED treatment led to a higher epilepsy recurrence rate.

The association between the type of AEDs and disease relapse was studied by Wolf et al. [10], Chadwick [11], Cardoso et al. [12], and Aktekin et al. [13]. There were 117 patients on monotherapy in the research of Wolf et al., and the main AEDs were valproic acid, carbamazepine, and phenobarbital/primidone. Twenty-one of the 46 patients who received valproic acid treatment had a relapse, 14 of the 37 patients who received carbamazepine treatment experienced a relapse, as well as 12 of the 23 patients who received phenobarbital/primidone treatment. In the study of Chadwick [11], there were 721 patients on monotherapy, including 237 patients on carbamazepine therapy, 72 patients on phenobarbital/primidone therapy, 184 patients on phenytoin therapy, and 228 patients on valproic therapy. At the third year after AED treatment withdrawal, relapse was noted in 80 of the 237 patients who received carbamazepine therapy, in 92 out of the 228 patients who received valproic acid therapy, in 21 of the 72 patients who received phenobarbital/primidone therapy, and in 73 of the 184 patients who received phenytoin therapy. In the study of Cardoso et al. [12], relapse was noted after AED treatment withdrawal in 4 of the 24 patients on phenytoin therapy, in 12 of the 41 patients on carbamazepine therapy, in 11 of the 27 patients on phenobarbital therapy, and on one of the two patients on valproate therapy. In the Aktekin et al.'s study [13], 12 of the 22 patients on carbamazepine therapy, eight of the 12 patients on valproate therapy, and four of the eight patients on phenytoin therapy experienced a relapse. We performed a meta-analysis of the recurrence between each of the drugs, and the results showed that the ORs were all between 0.7 and 1.4 ($P > 0.05$), and the heterogeneity was less than 50% in all subgroups, indicating that the type of AEDs did not influence the epilepsy recurrence rates.

In the studies by Choi et al. [15] and Kerling et al. [17], the decision to discontinue the AEDs was made after discussing the benefits of AED treatment withdrawal and the possibility of recurrence with the patients, and only with consent from the patients or their caregivers; therefore, their studies had a high selective bias when dividing the patients to AED treatment withdrawal or continuance groups, which means that the patients in the AED treatment continuance group had a greater risk of relapse than those in the AED treatment withdrawal group. This explained why in Choi et al.'s study, 29 of the 30 patients who were continued on AED treatment after being six months seizure-free relapsed; however, only 14 of the 40 patients in whom the AED treatment was withdrawn experienced a relapse. In Kerling et al.'s study, 10 of the 26 patients who were continued on AED treatment experienced a relapse, versus 8 of the 34 patients in whom AED treatment was continued. In the other five studies, the patients were not divided in such a highly selective way. The result of our meta-analysis of all seven included studies showed a high heterogeneity, and when we performed a subgroup meta-analysis of the five low-selection-bias studies, the heterogeneity was nonexistent. This phenomenon indicated that the source of the heterogeneity may be the selection bias in the studies of Choi et al. and Kerling et al.

Our study has some limitations. First, five studies included in this meta-analysis were cohort studies; they were not randomized and did not control for relevant factors, which may have caused the patients in the different groups to have different characteristics, leading to an unreliable result. Second, the patients in the studies we analyzed had different seizure-free periods and different follow-up duration; we did not analyze patients who had the same seizure-free periods, the same follow-up duration, and the same type of epilepsy.

Despite these limitations, this meta-analysis reports that in patients with epilepsy who are seizure-free, withdrawal of the AED treatment leads to a higher risk of seizure relapse than continuation of the treatment. Therefore, the decision to discontinue the AED treatment should be cautiously made. This meta-analysis also reports that the type of medications used prior to AED treatment withdrawal does not influence the epilepsy relapse rates.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106577.

Declaration of competing interest

None.

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